13. (twice amended) The method of claim [11] 10 wherein the syndecan is expressed [preferentially] in the areas of the hypothalamus responsible for the regulation of body weight and energy balance.

14. (amended) The method of claim [13] 10 wherein the [animal has incorporated therein a construct including] promoter is a cytomegalovirus promoter or functional portion thereof, and [including] the CMV intermediate/early enhancer.

15. (amended) The method of claim 14 wherein the [animal] rodent has the genotype FVB/N-TgN(synd-1).

Remarks

Claims 1-3, 5, 6, 10, and 11 have been amended to refer to a transgenic "rodent" rather than a transgenic "animal." Support for this amendment can be found at least on page 12:lines 11-15. Claim 5 has also been amended to depend from claim 1. Claims 4, 7-9, and 13-15 have been amended to remove reference to "preferential" expression.

The claimed subject matter

Claims 1 and 10 have been amended to define a transgenic rodent genetically engineered to express a syndecan, wherein the rodent develops maturity onset obesity. Claims 2 and 11 have been cancelled due to incorporation of the language into claims 1 and 10 relating to stable incorporation of the DNA sequence encoding the syndecan into the genome. Claims 3-6 and 13-15 are drawn to the rodent of claim 1 where the molecule is syndecan -1, where the construct includes the cytomegalovirus promoter or functional portion thereof including the CMV

intermediate/early enhancer, and where the rodent has the genotype FVB/N-TgN(synd-1), respectively. Claim 10 is drawn to a method for screening for compounds which can alter body weight by administering a compound to the rodent of claim 1, and observing whether there is a change in body weight over a period of time. Claim12 is drawn to the method of claim 10 where the syndecan is syndecan - 1. All of the claims are now limited to rodents rather than to all non-human animals, and incorporate the examiner's suggested language with the exception of the restriction to mice.

A declaration will be submitted shortly to demonstrate that those skilled in the art could make rats as claimed using the methods and reagents described in the application with respect to mice with an expectation of producing an animal developing maturity onset obesity.

Rejection under 35 U.S.C. § 103

Claims 7, 8 and 9 were rejected under 35 U.S.C. § 103 as obvious over Thomsen, et al., Proc. Natl. Acad. Sci. USA 81, 659-663 (1984), Boshart, et al., Cell 41, 521-530 (1985), and U.S. Patent No. 5,486,599 to Saunders. Claims 7-9 have been canceled, mooting this rejection. Applicants reserve the right to prosecute these claims in a later related application.

Rejections under 35 U.S.C.§ 112

Claims 1-3, 6, and 10-12 were rejected under 35 U.S.C. § 112, first paragraph, as not enabled for all transgenic animals. Claims 4, 5, 7-9, and 13-15 were rejected under 35 U.S.C. § 112,first paragraph, as not enabled for *preferential* expression in the hypothalmus. Claims 4 and 13-15 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite for use of the term

"preferential". These rejections are respectfully traversed if applied to the amended claims.

Claims 1, 3, 6, 10, and 12 have been amended to refer to rodents rather than to all non-human animals in an effort to facilitate prosecution. These claims are fully enabled for the reasons set forth below, although as noted above, additional evidence will be submitted shortly in support of this position.

The examiner's argument is based on the assertion that the transgenic rodent expressing syndecan, disclosed in the present application, is not representative of all transgenic animals expressing a syndecan. The basis for this assertion is that the art of making transgenic animals is unpredictable. The Examiner relies on four publications to support this assertion. These publications, discussed below, do not indicate the unpredictability of the art, but rather support the claimed subject matter.

Taurog et al., HLA-B27 Inbred and Non-inbred Transgenic Mice Cell Surface Expression and Recognition as an Alloantigen in the Absence of Human B2-Microglobulin, Journal of Immunology, 141:4020-23 (1988) ("Taurog").

Taurog discloses a transgenic mouse that expresses exogenous human HLA-B27. The expression of the human HLA-B27 is driven by human HLA-B27 promoter regions. A total of four mice were obtained that expressed the HLA-B27 at significant levels.

Hammer et al., Spontaneous Inflammatory Disease in Transgenic Rats Expressing HLA-B27 and Human B2m: An Animal Model of HLA-B27-Associated Human Disorders, Cell, 63:1099-1112 (1990) ("Hammer").

Hammer discloses transgenic rats that express human HLA-B27 from human promoters.

Mullins et al., Expression of the DBA/2J Ren-2 Gene in the Adrenal Gland of Trangenic Mice, EMBO. 8(13):4065-72 (1989) ("Mullins 1").

Mullins 1 discloses transgenic mice that express a *Ren-2* gene product from an exogenous construct. Expression of this *Ren-2* gene, however, is driven by the native mouse promoters.

Mullins et al., Fulmiant Hypertension in Transgenic Rats Harboring the Mouse Ren-2 Gene, Nature, 344:541-544 (1990) ("Mullins 2").

Mullins 2 discloses transgenic rats that express a *Ren-2* gene product from an exogenous construct. Expression of this *Ren-2* gene, however, is driven by the native mouse promoters. Furthermore, Mullins 2 discloses that they chose to make the transgenic rats because injection of purified mouse *Ren-2* into rats had previously been shown to cause severe hypertension (page 542 1st column).

The publications cited by the examiner are instances of a very specific type of transgenic animal, one designed to assess *transcriptional regulatory control*, not merely promote expression of a transgene. In Taurog, the transgene unit consists of human promoters, not mouse promoters or ubiquitous promoters. Thus, for the transgene to be expressed, transcription factors must be present within the mouse that recognize the human promoter region of the HLA-B27 gene. The very fact that this works at all is testament to the power of transgenic technology, not the unpredictability of trangenic technology, as asserted by the examiner. Hammer supports the presently claimed subject matter because in Hammer the transgenic rats express the transgene, as

would be expected when the transgene was expressed in the mouse. This *supports* the assertion that transgenic expression is expected within any species of the genus of rodents when the transgenic version of one species, mouse, has been shown to express the desired transgene product.

In Mullins 1 the transgene was driven by a mouse promoter, and the transgene was placed within a mouse. The transgene, *Ren-2*, was a gene which in a natural mouse existed as part of a gene cluster. This gene cluster was derived from gene duplication within the mouse. The mouse strain into which the transgene was placed lacked the *Ren-2* gene in the gene cluster. Thus, the only *Ren-2* expression in the transgenic mouse came from the transgene driven by the natural mouse *Ren-2* promoter region. This allowed the researchers to specifically study the expression of the *Ren-2* gene in the mouse.

The product of the transgene, Ren-2, was known to cause hypertension in rats when delivered exogenously in excess, i.e. directly into the blood system of the rat. The researchers predicted, in Mullins 2, that if the *Ren-2* gene product was overexpressed, via a transgene within a rat, that the same phenotype would exist. This is exactly what they found. The rat strain used to produce the transgenic rat containing the *Ren-2* transgene expressed its own endogenous form of rat *Ren-2*. Thus, the *Ren-2* transgenic rat produced an excess amount of Ren-2, which predictably produced the phenotype of hypertension. The mouse/rat transgene combination reported in Mullins 1 and Mullins 2 indicates the strong predictability of transgenic technology. Furthermore, the rat, a different species within the rodent genus, expressed the transgene, even

though the promoters used for transgene expression were mouse promoters, not rat promoters. Again, this shows the *predictability* of transgenic activity within the *rodent* genus, not the unpredictability.

Taurog, Hammer, Mullins 1, and Mullins 2 indicate that a successful showing of transgene expression in mice enables one of ordinary skill in the art to produce a transgenic rat (or other rodent) that expresses the same transgene. The genus rodents contains closely related species. Once constructs and transgene units are developed for transgene implantation in one of the species within the genus rodents are shown to function, other transgenic species within the genus can be made without undue burden or experimentation.

The specification clearly indicates to one of ordinary skill in the art that the technology will work within the genus rodents. For example, on page 12:lines 11-13 the application states, "[a]lthough the study described herein used mice, it would clearly be routine to apply the same technology to other rodents, such as rats or hamsters." Taurog, Hammer, Mullins 1 and Mullins 2 are strong evidence of the correctness of this statement. Hammer states, "Microinjection of eggs and transfer to day 1 pseudopregnant Sprague-Dawley females were carried out essentially as described for mice." Id. at 1110 Thus, the procedure for producing transgenic rats was essentially the same as the procedure for producing transgenic mice. In Mullins 1, the transgenic mice were produced by microinjection using the standard procedure of Hogan et al. Manipulating the Mouse Embryo, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY. (1986) ("Hogan"). Mullins 1 at 4071. In Mullins 2 the transgenic rats were produced using

microinjection, and the citation for the procedure used is Mullins 1. Mullins et al. at 542. Thus, the transgenic rats of Mullins 2 were produced the same way, using the same methods, as the transgenic mice of Mullins 1. The production of transgenic mice is predictive of future successful production of transgenic rats (or other species within the genus rodent).

The specification provides ample guidance for making transgenic mice. In fact, some of the methodology described in the present application is the same methodology described by Hogan, which is the same methodology used by Mullins 1. (see page 12:lines 30-33 of the specification and page 4071 of Mullin 1). This further supports the predictability of making transgenic rodents. Once the first transgenic rodent for a particular transgene is made, the techniques developed for that transgenic rodent are applicable to other rodent species.

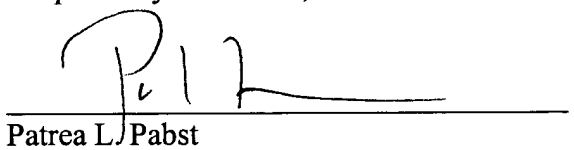
Rejection of claims 4, 5, 7-9, and 13-15

The constructs and transgenic animals defined by the claims will be preferentially expressed in the hypothalmus regardless of whether this limitation is recited in a claim. The preferential expression in the hypothalmus is inherent in the constructs. In an effort to facilitate prosecution, however, claims 4, 7-9, and 13-15 have been amended to delete the reference to "preferential", since it is believed there is agreement that the constructs are expressed in these tissues, and the only debate related to the question of whether this expression had been proven to be preferential. Thus, the rejection of claims 4, 5, 7-9, and 13-15 under 35 U.S.C. § 112, first paragraph, for allegedly failing to enable preferential expression in the hypothalmus, is mooted.

The rejection of claims 4, and 13-15 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite for the phrase "expressed preferentially in the hypothalmus," is also mooted.

Allowance of all of claims 1,3-6, 10, and 12-15, as amended, is earnestly solicited in view of the foregoing remarks.

Respectfully submitted,



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